

THE METABOLIC CAPABILITIES OF RAT COLON TISSUE SLICES EXPOSED TO THE COOKED-FOOD MUTAGEN/CARCINOGEN 2-AMINO-1-METHYL-6-PHENYLMIDAZO[4,5-*b*]PYRIDINE (PhIP). M.A. Malfatti, M.S. Connors¹, R.J. Mauthe, and J.S. Felton. Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, Livermore CA, 94551. ¹Department of Biological Sciences, San Jose State University, San Jose, CA, 95192.

The mutagenic potency of the cooked-food mutagen/carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) is highly dependent upon cytochrome P450 N-hydroxylation. A major target tissue for PhIP carcinogenesis in rodents is the colon. In the present study the metabolic capabilities of rat colon tissue exposed to PhIP were investigated in *Salmonella typhimurium* (strains TA98 and YG1024) and rat colon tissue slices. In the Ames/*Salmonella* assay, using rat colon S9 as the activating system, no mutations were evident from bacteria exposed to PhIP at any concentration tested. However, mutations were observed when bacteria was exposed to 2-aminoanthracene (2AA) indicating there was sufficient P450 activity in the colon S9 to activate 2AA but not PhIP. In rat colon slice preparations the sulfotransferase inhibitors pentachlorophenol (PCP) and 2,6-dichloro-4-nitrophenol (DCNP) were used to modulate DNA adduct and metabolite formation. Incubations of 3-methylcholanthrene induced colon slices dosed with ³H-PhIP (50 μ M) produced no detectable metabolites. However, incubations of uninduced slices exposed to 10 μ M of the reactive intermediate, ³H-2-(hydroxyamino)-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (N-hydroxy-PhIP), produced a single detectable metabolite, a glucuronide conjugate of N-hydroxy-PhIP. This metabolite decreased when PCP or DCNP was added to the incubation medium. DNA adducts were detected in colon slices exposed to N-hydroxy-PhIP at approximately 49 adducts per 10⁷ nucleotides. Interestingly, when PCP was added to the incubation mixture a dose dependent increase in DNA adduct levels was detected while DCNP produced a dose dependent decrease in adducts. Since these inhibitors are thought to have similar mechanisms with regards to sulfotransferase inhibition the inverse relationship in DNA adduct levels due to PCP or DCNP treatment is at present unexplainable. The formation of DNA adducts and metabolites from colon slices exposed to N-hydroxy-PhIP but not PhIP imply that there is insufficient P450 activity in the rat colon to activate PhIP to hydroxylated metabolites, suggesting the rat colon is a site of phase II metabolism for PhIP. (This work was performed under the auspices of the U.S. DOE by LLNL under contract W-7405-Eng-48 and supported by NCI grant CA55861)